Applicants herein amend claim 1 to recite stabilizers comprising "one or more saccharides as a mixture with more than 0.5 mol/l of each of two or more amino acids," one of which is glutamate, and to recite that the stabilized protein preparation is "an aqueous protein solution." Applicants note that "glutamate" is a glutamic acid salt, and thus falls within "glutamic acid and its salts." Claim 14 is amended similarly to claim 1. The paragraph format of claims 1 and 14 is also revised for easier readability. These amendments are supported by the application as a whole, for example, at page 6, lines 1-6, and in the example at page 6, line 18, to page 8, line 4.

New claim 17 is also added to the application to reflect the embodiment shown at page 7, Batch 2. Because claim 17 is a composition claim and depends on claim 1, Applicants submit that it should be examined with claims 1-6, 8-9 and 14-16.

Applicants submit that the amendments to claims 1 and 14 and new claim 17 do not introduce new matter, or require a further search of the art, and respectfully request their entry.

Objections to the Specification

The Office objected to the arrangement of the specification under 37 C.F.R. 1.77(b) for lacking specific section headings, though acknowledged that these headings are "preferred" but not required. (Office Action at page 3.)

The instant application is based on Application No. 100 22 092.4, originally structured for filing in the German patent office. Applicants demur from adding section headings not present in the original German application, because characterization of certain parts of the specification as "Field of the Invention" or "Background of the Invention" can lead to inadvertent admissions against interest when an application was

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1300 I STREET, N. W.
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not originally structured to accommodate these divisions. For example, an application originally structured without headings may interweave discussions of the prior art with comparisons to the claimed invention, upon which the inventors seek to rely for support. If such a segment of the specification were to be labeled "Background of the Invention" or "Description of the Related Art," an applicant might be prevented from relying on it in support of the claims. More importantly, these headings are merely preferred, and are not required by statute. Therefore, to avoid possible error, Applicants respectfully request that this objection be withdrawn.

The Office also objected to the specification under 37 C.F.R. § 1.75(d) for allegedly reciting "more than 1.5 g/ml" only in original claim 5. (Office Action at page 3.) Contrary to the Office's statement that this phrase "has no support in the specification," originally filed claims are not separate from the specification, but are an integral part of it. *See* 35 U.S.C. § 112, second paragraph, ("The specification shall conclude with one or more claims . . .") Therefore, claim 5 is fully supported by the application as filed, and there is no need to explicitly re-state its contents elsewhere in the text of the specification. In any case, the paragraph at page 6, lines 1-6, provides appropriate antecedent support for this phrase. ("Mixtures of a saccharide in a concentration of more than 1.5 g/ml with one or more of the abovementioned amino acids in concentrations of over 0.5 mol/l . . .") Therefore, Applicants demur from amending the specification, as the Office suggests, and respectfully request the withdrawal of this rejection.

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1300 I STREET, N. W.
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Rejections under 35 U.S.C. § 102(b)

First, the Office rejected claims 1-6, 8, and 14-15, alleging that they are anticipated by U.S. Patent No. 4,623,717 ("Fernandes"). (Office Action at page 4.) Second, the Office rejected claims 1-2, 6, 8, and 14-15, alleging that they are anticipated by European Patent No. 0077355 B1 ("Thomas"). (Office Action at pages 4-5.) Applicants traverse both of these rejections in light of the amendments to claim 1. Fernandes and Thomas do not teach stabilizers comprising the specific combination of amino acids "more than 0.5 mol/l of each of two or more amino acids," including glutamate, required in claim 1.

Fernandes teaches lower total amino acid concentrations than those of the present claims. The amino acid concentration of Fernandes's composition is limited in its total amount to "in the range of about 0.05 M to about 0.8 M, preferably about 0.1 M to about 0.65 M," while even smaller amounts are emphasized in the examples of Fernandes, as discussed below. (Fernandes at col. 5, lines 22-40, and claim 15.) In contrast, claim 1 as amended requires that the amino acids have a total concentration of more than 1.0 mol/l because the claim requires "more than 0.5 mol/l of each of two or more amino acids" chosen from the recited list in the claim. Claim 14, as amended, requires that the amino acids have a total concentration of more than 1.6 mol/l because the claim requires "more than 0.8 mol/l of each of two or more amino acids" chosen from the recited list. Dependent claims 8 and 15 also require the addition of more than 0.5 mol/l or more than 0.8 mol/l of glycine and/or glutamine. Therefore, the concentration ranges of amino acids recited in Fernandes and in Applicants' claims do not overlap.

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In addition, unlike Fernandes, the compositions of claims 1 and 14 require that one of the chosen amino acids is glutamate. While Fernandes includes a list of amino acids that one "may employ" in its invention, there is no requirement to employ glutamate. (Fernandes at col. 5, lines 21-40.) Instead, Fernandes's text and working examples focus entirely upon arginine, lysine, and glycine, which are described as "preferred" amino acids. (Fernandes at col. 5, lines 38-40, and at Examples 2-7, cols. 9-12.)

Thomas does not anticipate Applicants' claims for similar reasons. Thomas recites that its stabilizers "include albumin, glycine, proline, mannitol, and sorbitol," or "glycine, proline, or other amino acid." (Thomas at page 4, line 47, and page 14, claim 11.) Neither glycine nor proline is included in Applicants' claims 1 or 14. Further, the genus of "other amino acids" in Thomas comprises at least hundreds of compounds with a general amino acid backbone NH_3-CHR-COO^- and any possible side-chain R. Therefore, one of ordinary skill in the art cannot "at once envisage" from Thomas's disclosure the claimed genus, or its requirement of glutamate. *See* M.P.E.P. § 2131.02. Indeed, to arrive at Applicants' claimed genus, one would have to pick and choose from an enormous array of possible genera. Even if "amino acids" were restricted to the biological twenty varieties, one would have to choose from every possible combination of eight of those twenty amino acids in order to obtain a genus similar to that which Applicants claim.

Finally, Thomas refers to a dry composition rather than to an "aqueous protein solution," as in claims 1 and 14. For example, Thomas states that "[t]he enzyme compositions and biological indicators as further described herein must be heat treated

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in the dry state," meaning "less than about 5% water by weight." (Thomas at page 7, lines 48-50.) Thus, Thomas's "compositions may be powder, cake or other suitable form." (*Id.*; *and see* Thomas at page 4, lines 14-19, and page 8, lines 32-40, and at claim 1, page 14.)

Therefore, neither Thomas nor Fernandes anticipates Applicants' claims, and Applicants request the withdrawal of these rejections.

Rejections under 35 U.S.C. § 103(a)

The Office rejected claims 1, 7, 9, 14, and 16, as allegedly obvious over Fernandes in view of U.S. Patent No. 4,960,757 ("Kumpe"). (Office Action at pages 5-6.) Applicants traverse this rejection.

In order for a claim to be *prima facie* obvious, there must be a motivation to combine the teachings of the cited references that is supported by substantial evidence. M.P.E.P. § 2143; *In re Lee*, 61 U.S.P.Q.2d 1430, 1435 (Fed. Cir. 2002); *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Moreover, motivation requires that there be a desire to combine the references, not just that the combination be feasible. *Winner Intl. Realty Corp. v. Wang*, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000). This motivation or desire must be found in the in the teachings of the prior art, not in an applicant's specification. M.P.E.P. § 2143. As explained below, there is no suggestion in the cited art that it would be desirable to modify the teachings of Kumpe and Fernandes in such a way that one would obtain Applicants' claimed preparations.

As described above, Fernandes does not teach or suggest the particular list of amino acids recited in claims 1 or 14. Instead, Fernandes focuses on the use of glycine, which is not listed in claim 1 or 14, as well as on lysine and arginine.

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(Fernandes at Examples 2-7, cols. 9-12.) The only way to arrive at the claimed combination of amino acids in light of Fernandes's teachings is to use hindsight from Applicants' disclosure, which is impermissible. M.P.E.P. § 2143.

Even more importantly, all of the claims require that one of the chosen amino acids is glutamate. For example, Batch 2, at page 7, shows that glutamate in addition to another amino acid, such as arginine, results in extremely high protein stability compared with a prior art combination using glycine (Batch 1), even when calcium chloride is also added as a stabilizer to the prior art combination. Fernandes makes no suggestion that glutamate should be used to increase the stability of a protein preparation.

Kumpe does not remedy this deficiency of Fernandes. While Kumpe's claim 1 mentions "an amino acid or mixture of amino acids," the only amino acid mentioned by name in Kumpe is glycine, which is also used in Kumpe's example. (Kumpe at col. 2, lines 1-4, and col. 3, lines 10-31.) Again, glycine is not among the amino acids listed in either claim 1 or claim 14. Kumpe's recitation of "amino acid or mixture of amino acids" presents a nearly infinite possibility of compounds and mixtures of compounds, as the remarks above with respect to Thomas illustrate. Therefore, Kumpe as a whole does not suggest the particular, claimed genus of amino acids, which must include glutamate.

Because nether Kumpe or Fernandes alone suggests the claimed genus of amino acids, including glutamate, neither does their combination provide a motivation to choose the claimed genus. Indeed, on the contrary, the combination of Fernandes and Kumpe suggests the desirability of preparing a formulation similar to the prior art Batch 1 described at page 7 of the specification, which includes sucrose, glycine and a

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calcium salt. Applicants have shown that this preparation results in lower protein stability than a combination of sucrose, glutamate and arginine (Batch 2).

In addition, Applicants note that Fernandes as a whole focuses on the use of amino acid concentrations below 0.5 mol/l each. In contrast, claim 1 requires "more than 0.5 mol/l of each of two or more amino acids" chosen from the list recited in the claim. Claim 14 requires even higher quantities, while claims 8 and 15 require the addition of glycine and/or glutamine as well. All of Fernandes's working examples point out that low concentrations of lysine or glycine are preferable. (Fernandes at col. 5 and cols. 9-12.) In fact, examples 2-7 all use at most 0.5 mol/l of a single amino acid, or no more than 0.62 mol/l of two amino acids including glycine. (Fernandes at cols. 9-12, tables.) For example, at col. 9, lines 39-55, the patent states that data obtained for preparations containing 0.3 mol/l glycine alone, "indicate that the use of higher concentrations of sucrose, representative of concentration of sugars and reduced sugars, in combination with a lower concentration of glycine as the amino acid stabilizer against heat than was heretofore known, provides for advantageous recovery of [Factor VIII]." A similar comment is provided at col. 10, lines 46-59, in connection with the use of 0.3 mol/l glycine and 0.32 mol/l lysine. At col. 11, lines 21-25, Fernandes further notes that "a combination of a mixture of 0.16 M glycine and as low as 0.04 M lysine with 1.2 g/ml of sucrose affords advantageous stability to heat." Fernandes at col. 11, lines 49-55 points out the advantage of using "as low a concentration as 0.3 M of glycine alone, or as low a concentration as 0.05 M arginine alone, or a concentration of 0.15 M glycine together with 0.05 M arginine." Finally, the table in Example 7 shows the use of 0.5 M arginine alone or 0.5 M lysine alone. (Col. 12, lines 5-20.) Thus,

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Fernandes as a whole teaches that one should use no more than 0.5 mol/l of one amino acid or 0.62 mol/l of two amino acids to prepare a stabilized protein preparation. As a result, Fernandes does not teach the desirability of increasing the amino acid concentration above 0.5 mol/l, as Applicants have done, and, in fact, teaches away from it by insisting that these low concentrations give "advantageous stability."

Finally, as to the addition of calcium salts in claims 7, 9, and 16, Kumpe teaches their use only with glycine, rather than with any of the amino acids recited in claim 1. In fact, as mentioned previously, Kumpe's teachings are similar to the prior art Batch 1 shown at page 7 of the specification, which provides inferior stabilization compared to Applicants' sucrose, glutamate, and arginine mixture.

To support its argument that claims 7, 9, and 16 are *prima facie* obvious in light of Kumpe and Fernandes, the Office cited *In re Kerkhoven*, 205 U.S.P.Q. 1069 (C.C.P.A. 1980). (Office Action at page 6.) Yet, *Kerkhoven* is not applicable to the present facts. In *Kerkhoven*, the applicant sought to combine two complete prior art inventions without altering either of them. Thus, no ingredients needed to be changed or modified and all that was necessary was to add them together. In contrast, simply combining the actual compositions taught by Kumpe and Fernandes would not produce Applicants' present claims 7, 9, or 16 because one would need to modify the teachings of both references to use a different combination and amount of amino acid stabilizers than those references teach.

The Federal Circuit has repeatedly stated that to make a *prima facie* case of obviousness, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected *these components in the*

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manner claimed." *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002), quoting *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (emphasis added). Therefore, the Office bears the burden to provide substantial evidence showing why the teachings of Fernandes and Kumpe would lead one of ordinary skill in the art to choose the particular combination of amino acids recited in Applicants' claims. *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Moreover, the Office cannot meet this burden by simply showing that a different combination would be feasible. *Winner Intl. Realty Corp. v. Wang*, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000). The combination must be desirable, and the desirability of the claimed combination must be expressed in the prior art teachings, not in Applicants' specification. M.P.E.P. § 2143.

Fernandes and Kumpe do not show that it would be desirable to use a combination of amino acids including glutamate and the others listed in claim 1 in concentrations of more than 0.5 mol/l each, because their combined teachings as a whole suggest that excellent stabilization may be obtained with low concentrations of glycine. Thus, the combination of Fernandes and Kumpe does not render any of the instant claims obvious, and Applicants request that this rejection be withdrawn.

The Office also rejected claims 1, 3-5, 7, 9, 14, and 16, as allegedly obvious over Thomas in view of Fernandes and Kumpe. (Office Action at pages 6-8.) Applicants also traverse this rejection.

As explained above, the combination of Fernandes and Kumpe does not render claim 1 or any of its dependent claims obvious. Moreover, Thomas is not applicable to the present invention, which is an "aqueous protein solution," because Thomas refers to a dry composition. (Thomas at page 4, lines 14-19, page 7, lines 48-53, and page 8,

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lines 32-40.) Such a composition is expected to have different stabilization requirements because the proteins are removed from their normal aqueous environment and are subjected to different environmental stresses.

In addition, like Kumpe, Thomas teaches stabilizers (albumin, glycine, proline, mannitol, and sorbitol) that do not overlap with any of those in claim 1. (Thomas at page 4, line 47.) Thus, Thomas, in combination with Fernandes and Kumpe, does not provide motivation for one of skill in the art to select the amino acids listed in claim 1. Thomas mentions only "glycine, proline, or other amino acid." (Page 14, claim 11.) As discussed above, the recitation of "other amino acid" does not lead one to select the particular list claimed in instant claim 1 because there are hundreds of known amino acids available to those in the art. Moreover, all three of these patents continuously suggest that glycine is the preferred amino acid, either by reciting it by name or by using it in their working examples. Glycine is not among the amino acids listed in independent claims 1 or 14. The focus on glycine does not provide one of ordinary skill in the art with a desire to substitute a different amino acid, such as glutamate. In fact, it teaches away from so doing. For all of these reasons, the combination of Thomas, Fernandes, and Kumpe does not render any of the instant claims obvious, and Applicants respectfully request the withdrawal of this rejection.

Request to Rejoin Claims 10-13

Applicants respectfully request that process claims 10-13 be rejoined to the composition claims 1-9 and 14-17 in accordance with 37 C.F.R. § 1.141 and M.P.E.P. § 821.04.

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& DUNNER, L.L.P.
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Section 821.04 of the M.P.E.P. states that if an applicant elects to prosecute a claim to a product, as here, withdrawn process claims that "depend from or otherwise include all the limitations of the allowable product claim will be rejoined." Claims 10-13 are such process claims because all of them depend from composition claim 1. Therefore, Applicants request that once claims 1-9 and 14-17 are deemed allowable, claims 10-13 be rejoined to this application.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: January 29, 2003

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

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FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
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APPENDIX TO AMENDMENT OF JANUARY 29, 2003

Version Showing Marked-Up Changes

AMENDMENTS TO THE CLAIMS:

1. (Amended) A stabilized protein preparation, which is protected against a loss of activity during pasteurization by the addition of stabilizers which comprise:

one or more saccharides as a mixture with more than 0.5 mol/l of each of two [one] or more amino acids chosen from arginine, lysine, histidine, phenylalanine, tryptophan, tyrosine, aspartic acid and its salts, and glutamic acid and its salts; wherein one of said amino acids is glutamate; and

wherein the stabilized protein preparation is an aqueous protein solution and contains no antithrombin III.

14. (Amended) A stabilized protein preparation, which is protected against a loss of activity during pasteurization by the addition of stabilizers which comprise:

more than 1.5 g/ml of one or more saccharides as a mixture with more than 0.8 mol/l of each of two [one] or more amino acids chosen from arginine, lysine, histidine, phenylalanine, tryptophan, tyrosine, aspartic acid and its salts, and glutamic acid and its salts;

wherein one of said amino acids is glutamate; and

wherein the stabilized protein preparation is an aqueous protein solution and contains no antithrombin III.

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1300 I STREET, N. W.
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